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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/676,933	09/30/2003	Eugeni Namsaraev	502.02US	7872

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EXAMINER	
MAKAR, KIMBERLY A	
ART UNIT	PAPER NUMBER
1636	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/676,933	NAMSARAEV, EUGENI	
	Examiner	Art Unit	
	Kimberly A. Makar	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *15-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :12/12/03;4/05/04;3/28/05;4/25/05;5/05/05;07/28/06.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group I, claims 1-14 in the reply filed on 11/02/06 is acknowledged.

2. Claims 15-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/02/06.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1 and 13 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 4 of

copending Application No. 11/250,986. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1 and 13 are a genus of claims 1 and 4 of copending application No. 11/250986. Claims 1 and 13 of the instant application read on a method of constructing a polynucleotide, comprising ligating a first and second oligonucleotide to a scaffolding complex (claim 1) wherein a sampled population (the first and second oligonucleotides to be ligated) were the products of two previous oligonucleotide synthesis reactions themselves (claim 13). The species of claim of application 11/250986 reads on making a first and second ligatable oligonucleotide population and ligating them to a scaffolding complex (claim 1) and (claim 4). It is common practice to imbed restriction endonuclease sites (cleavage sites) into the overhangs of ligation amplification oligonucleotides to aid in ligation reactions (see Lebedenko et al (Method of Artificial DNA Splicing By Directed Ligation (SDL), Nucleic Acids Research, 1991. 19(24):6757-6761)). Thus it would have been obvious for a skilled artisan to modify the genus claims of the instant application by adding restriction endonuclease sites, cleaving the products and then using the products in a ligation amplification reaction, and ligating them to the scaffold duplex. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Objections

5. Claim 14 is objected to because of the following informalities: Claim 14 misspells the word "first" as "fist". Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the phrase, "conditions in which hybridization of said first and second oligonucleotides to the single-stranded regions a the termini of said scaffold is unstable." This phrase is not defined in the specification. The specification conditions are not stated. The only real condition that the specification seems to states is that, "The only requirement for unstable annealing between the scaffold and the first and second oligos is that the ligation temperature be high enough to prevent stable duplex formation." (page 7, paragraph 0018). However, this in itself is not a definition of conditions in which hybridization is unstable. There is also a ligation challenge experiment, used to test stability (page 27, paragraph 0078). However, there is no delimitation as to demarcate stable from nonstable. The stability of hybridization is affected by base pair matching, base pair content, pH, salinity, temperature, etc. It is unclear from the specification what "conditions in which hybridization of said first and

second oligonucleotides to the single-stranded regions a the termini of said scaffold is unstable." The possibility arises that 100% complementarity of one oligonucleotide complex would be less stable than one comprising 5% base pair mismatches depending upon pH, temperature, length of the oligonucleotides, etc. As such, a skilled artisan would be unable to determine the metes and bounds of the claimed invention.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-7, and 10-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Sorge et al (US Patent No. 5,858,731). Claims 1-7, and 10-14 recite a method of constructing a product polynucleotide using populations of truncate-containing oligonucleotide synthesis products, the method comprising: partially duplexing a scaffold oligonucleotide of subtemplate length having a first terminus and a second terminus with a central oligonucleotide that has a 5' terminus and a 3' terminus, such that a single-stranded region is left at both the first and second termini of the scaffold oligonucleotide; and ligating a first and a second oligonucleotide, respectively, to the 5' and 3' termini of said central oligonucleotide by sampling respective first and second populations of truncate-containing oligonucleotide synthesis products with the single-

stranded regions at the termini of said partially duplexed scaffold oligonucleotide, said sampling being performed in the presence of a ligase under conditions in which hybridization of said first and second oligonucleotides to the single-stranded regions at the termini of said scaffold oligonucleotide is unstable, and in which hybridization of said central oligonucleotide to said scaffold oligonucleotide is stable, wherein the first oligonucleotide includes a region perfectly complementary in sequence to the single-stranded region at the first terminus of said scaffold oligonucleotide and the second oligonucleotide includes a region perfectly complementary in sequence to the single-stranded region at the second terminus of said scaffold oligonucleotide (claim 1). The method is further limited wherein said partial duplexing and said ligating are performed in a single step (claim 2) and further comprising a step of size separating the product polynucleotide from the scaffold oligonucleotide (claim 3). The method is further limited wherein each of the single-stranded regions at the termini of the scaffold oligonucleotide is no more than 10 nucleotides long (claim 4) or no more than 7 nucleotides long (claim 5) or no more than 5 nucleotides long (claim 6). The method is further limited wherein the ligating step includes a temperature of at least 30° C (claim 7). The method is further limited wherein the product polynucleotide extends at least 10 nucleotides (claim 10) or at least 25 nucleotides (claim 11) or at least 75 nucleotides beyond each of the termini of the scaffold oligonucleotide (claim 12). The method is further limited wherein said first sampled population includes the products of a first plurality of oligonucleotide syntheses, the full-length synthesis products of at least two of said first plurality of syntheses being different in sequence, and said second population includes the

products of a second plurality of oligonucleotide syntheses, the full-length synthesis products of at least two of said second plurality of syntheses being different in sequence (claim 13) and wherein the scaffold oligonucleotide is partially duplexed to the central oligonucleotide, such that a single-stranded region is left at both the fist and second termini of the scaffold oligonucleotide, prior to contacting the scaffold and central oligonucleotides with the first and second oligonucleotides (claim 14).

10. Sorge et al (US Patent No. 5,858,731) teaches a method of generating polynucleotides from hybridization and ligation of at least one hybridization complex to another hybridization complex (see abstract). Sorge teaches the construction of hybridization duplexes (scaffold oligonucleotides) to one another (see scheme I and scheme II). Sorge teaches that the complexes are up to 12 nucleotides in length (column 8, lines 19-25). Sorge teaches that the hybridization complexes can have 5' or 3', or both overhangs (column 14, lines 7-18). Sorge teaches the use of degenerate nucleotides at any one or all of the complex nucleotides, which destabilize the hybridization between complexes (column 3, line 1-11). Sorge teaches, "it is important to note that upon hybridization and ligation of the non-annealing oligonucleotides, the oligonucleotides where N positions destabilize the complex are selected away, and the ligation reaction product is enriched for certain oligonucleotides." (column 3, lines 46-50). Thus Sorge teaches that hybridization of the duplexes to one another occur under conditions for hybridization that are unstable.

11. Sorge teaches that the complexes can be hybridized and ligated to each other, both upstream and downstream. He teaches, "All duplexes of the invention have two

domains: at least one overhang, and a region of complementarity between the oligonucleotides of the duplex. Two overhangs arise, for example, wherein two 8mer oligonucleotides are offset in complementarity to form a duplex have two nucleotides in an overhang at each termini. In one preferred embodiment, the oligonucleotide of the duplex providing the overhang is adapted for ligation to the terminal 3' nucleotide of another oligonucleotide to direct ligation between two duplexes, designated upstream and downstream duplexes to connote that upon ligation, a single, ligated oligonucleotide of preselected sequence is formed" (column 14, lines 7-18). He also teaches multiple complexes can be ligated together, including three, four, or more complexes (column 4, lines 1-7). Sorge teaches that the overhang is "a region of single strandedness at a termini of a double-stranded (duplex) oligonucleotide molecule that is typically available to hybridize to a complementary single-stranded overhang" (column 7, lines 17-20). Sorge teaches the generation of libraries for the formation of the ligation duplexes. "thus, each species of this library has a nucleotide sequence such that it can form, upon complementary hybridization with another species of the library, a double-stranded (ds) duplex DNA molecule having an over-hang on at least one terminus" (column 9, lines 16-20).

12. Sorge teaches that the ligation and hybridization (partial duplexing) are performed in a single step (column 24, lines 48-49). He also teaches that the polynucleotides can be separated from smaller fragments (column 25, lines 25-33). Sorge further teaches that the overhang is on either end of the complex is between 1 to

3 nucleotides in length (column 15, line 5). Sorge teaches a ligation temperature of at least 37°C (column 25, lines 11-17).

13. Since Sorge teaches the additive nature of the ligation hybridization method on oligonucleotides formed from previously ligated rounds of amplification and ligation would thus exceed at least 10, 25, and 75 nucleotides beyond the 1-3 nucleotide overhang limit. Sorge teaches that, "by selection of "nested" overlapping oligonucleotides that serve as templates for one another, one can build 18mers, 22mers, 24mers, 30mers, and the like" (column 12, line 58 – column 13 line 42). The hybridization of three 30mers would result in a complex that is 90 nucleotides in length, stemming from the smaller duplex ligations. By teaching the mixing of duplex formations, through libraries as mentioned above, he teaches a method in which in a first plurality of oligonucleotide synthesis (comprised of the full length synthesis products different in sequence) and a second plurality of oligosynthesis (comprises of full length synthesis products different in sequence) are pooled to comprise a first sampled population. Additionally, by pooling different preformed duplexes (scaffolds) with at least one degenerate nucleotide with a additional duplexes with different sequences with 3' and 5' overhangs, he teaches that the scaffold oligonucleotide is partially duplexes to the central oligonucleotide, such that a single stranded region is left at both the first and second termini of the scaffold oligonucleotide, prior to contacting the scaffold and central oligonucleotides with the first and second oligonucleotides. Thus Sorge teaches the claimed invention.

Claim Rejections - 35 USC § 103

14. Claims 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sorge at al (US Patent No. 5,858,731) as applied to claim 1 above, and further in view of Baraney et al (US Patent No. 5,494,810). Claims 8-9 recite a method of constructing a product polynucleotide using populations of truncate-containing oligonucleotide synthesis products, the method comprising: partially duplexing a scaffold oligonucleotide of subtemplate length having a first terminus and a second terminus with a central oligonucleotide that has a 5' terminus and a 3' terminus, such that a single-stranded region is left at both the first and second termini of the scaffold oligonucleotide; and ligating a first and a second oligonucleotide, respectively, to the 5' and 3' termini of said central oligonucleotide by sampling respective first and second populations of truncate-containing oligonucleotide synthesis products with the single-stranded regions at the termini of said partially duplexed scaffold oligonucleotide, said sampling being performed in the presence of a ligase under conditions in which hybridization of said first and second oligonucleotides to the single-stranded regions at the termini of said scaffold oligonucleotide is unstable, and in which hybridization of said central oligonucleotide to said scaffold oligonucleotide is stable, wherein the first oligonucleotide includes a region perfectly complementary in sequence to the single-stranded region at the first terminus of said scaffold oligonucleotide and the second oligonucleotide includes a region perfectly complementary in sequence to the single-stranded region at the second terminus of said scaffold oligonucleotide (claim 1). The

method is further limited wherein the conditions of the ligating step include a temperature of at least 42°C (claim 8) and at least 50°C (claim 9).

15. Sorge teaches a method of constructing a oligonucleotide product comprising a partially duplexed scaffold oligonucleotide with 5' and 3' overhangs that is hybridized and ligated to oligonucleotides that are complementary to the 5' and 3' overhangs in the presence of ligase at a temperature of at least 37°C (see above). Sorge does not teach that the ligation temperature is at least 42°C or 50°C.

16. Baraney et al (US Patent No. 5,494,810) teaches a thermostable ligase for the use in ligase chain reaction assays, designed specifically to work in conditions where there is a difference in the specific sequences between the complexing oligonucleotides (see abstract). Baraney teaches that as the number of mismatches, either through substitution, deletion or addition, the use of a common ligase, such as T4 ligase, results in a high degree of non-specific ligation products, resulting in high background levels (column 2, lines 38-43). He teaches that raising the temperature of the reaction denatures the ligase, requiring the addition of more T4 ligase for subsequent cycles of amplification (column 2, lines 44-56). Baraney teaches DNA at a temperature between 45-65°C is still able to hybridize to complementary sequences (column 3, lines 25-28) and that his thermostable ligase would be able to ligate different oligonucleotide substrates at temperatures ranging from 45°C to 90°C (column 10, lines 20-24 and lines 44-48). Baraney also teaches the use of a thermostable ligase at 42oC (column 13, lines 54-64).

17. A skilled artisan would have been motivated to combine the teaching of Sorge on a method of constructing a oligonucleotide product comprising a partially duplexed scaffold oligonucleotide with 5' and 3' overhangs that is hybridized and ligated to oligonucleotides that are complementary to the 5' and 3' overhangs in the presence of ligase at a temperature of at least 37°C with the teaching of Baraney on a thermostable ligse able to reduce nonspecific ligation reaction background levels on oligonucleotide complexes comprising nucleotide mismatches because while Sorge teaches degenerate nucleotides as one method of increasing the specificity to the hybridization between complexes, the use of a thermostable ligase able to act at a temperature which reduces nonspecific hybridization, but still allows complementary hybridization would allow an even greater specificity to the construction of the oligonucleotide amplification of the distinct 3' and 5' ends. It would have been obvious to the skilled artisan to combine the ligation method of Sorge with the thermostable ligase of Baraney because the improvement of the method at a higher temperature would result in a reduction of improperly formed duplex ligations – thus reducing the amount of purification and increasing overall yield of the amplification product. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

Conclusion

18. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Makar, Ph.D. whose telephone number is 571-272-4139. The examiner can normally be reached on 8AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kam/12/18/06

DAVID GUZO
PRIMARY EXAMINER